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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/202,463	08/19/1999	JAN BRUNDELL	100096.401	2926

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EXAMINER

TURNER, SHARON L

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/202,463

Applicant(s)

BRUNDELL ET AL.

Examiner

Sharon L. Turner

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-29 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 10-28-03 has been entered.
2. The amendment filed 10-28-03 has been entered into the record and has been fully considered. Claims 19-29 are pending.

Claim Objections

3. Claims 25-29 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 25-29 lack clear antecedent basis within claim 19. In particular, claim 19 recites monoclonal antibodies specific for a peptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3 whereas claims 25-29 appear to refer to an antibody specific for SEQ ID NO:2 and in particular to residues 20-35 and 6-38 of SEQ ID NO:2 and to residues 5-10 of SEQ ID NO:3. However, the claims are dependent and must share all the characteristics of the parent claim. Yet in instant case, the claims further limit antibodies not recited in the parent claim. Thus, the dependent claims do not further

limit the antibodies of the independent claims to which they refer. Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 19-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite a method of determining the presence of human S-100beta polypeptide via reacting with monoclonal antibodies specific for peptides having particular amino acid sequences. In addition, the claims recite that the first and second peptides are not identical. Applicants are attempting to recite the specificity of the antibodies by the characteristics of the target peptide in contrast to the characteristics of the epitope to which the antibody is reactive to or specific for. For example, consider that S100beta is the peptide to be detected. The S100beta peptide comprises both the sequence of SEQ ID NO:2 as well as the sequence of SEQ ID NO:3. Thus, the peptide that Applicants are detecting are the same peptide of S100beta. Thus the peptide detected (the second peptide and the first peptide) are to be identical. However, the claim specifies the converse, "that the second peptide not be identical to the first peptide". If this is the case it is unclear to the artisan what peptide Applicant is to be detecting via sandwich as the S100 beta peptide is the peptide to be detected and it "has" both the sequences of SEQ ID NO:2 and 3. Alternatively, the assay is merely one

where S100beta is apparently detected using two monoclonals, but it is not essential that the antibodies bind to the same protein for detection, in other words the peptide solution would provide multiple peptides and it would be of no relevance that the epitope was the same so long as one of each type of antibody bind to a molecule of s100 beta protein.

It appears via the specification and Applicant's arguments as to the art, that their intention is to recite monoclonal antibodies specific to the epitopes of SEQ ID NO:2 and SEQ ID NO:3. However, by the use of the language "having" Applicant's have directed that the epitope or specificity of the antibodies is not pertinent, i.e., to that of SEQ ID NO:2 and 3. The antibodies are merely required to bind to peptides "having" these sequences. While it is inclusive of S100beta it would also pertain to any variant so long as it "had" the noted sequences, regardless of the sequence or portion to which the antibody bound to. Applicants are suggested to recite the antibody or epitope specificity desired. It is further noted to the sandwich assay that claim 19 is not noted to provide for the labeling of any particular antibody for detection.

6. Claims 25-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25-29 lack clear antecedent basis within claim 19. In particular, claim 19 recites monoclonal antibodies specific for a peptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3 whereas claims 25-29 appear to refer to an antibody specific for SEQ ID NO:2 and in particular to residues 20-35 and 6-38 of SEQ ID NO:2 and to residues 5-10 of SEQ ID NO:3. There is

insufficient antecedent basis for this limitation in the claim because the claims actually further limit a monoclonal antibody specific for a peptide having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:3.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 19-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Eldik et al., PNAS 81:6034-38, October 1984, Okada et al., US 5,320,944 June 14, 1994, and Shibue et al., 5,240,863 August 31, 1993.

Van Eldik et al., teach monoclonal antibodies specifically reactive to S100 beta. S100beta has the amino acid sequence of SEQ ID NO:2 and SEQ ID NO:3 and the

particular epitopes within SEQ ID NO: 2, residues 6-38 or 20-35 and SEQ ID NO:3 residues 5-10 as newly claimed. The antibodies are generated using purified bovine brain S100beta immunogen as set forth. The antibodies specifically react with S100 beta as determined via ELISA (enzyme linked immunosorbant assay) assay, see in particular Abstract, Production of Monoclonal Antibodies and ELISA, p. 6034-6035. The procedure generated two isolated clones each producing different monoclonal antibodies designated 1A1 and 4D4 which are specific for S100beta as set forth at pp. 6035, column 2, RESULTS, first paragraph. The antibodies cross-react with S100beta from human, rat, and chicken brain but do not react with any S100alpha-like proteins examined (bovine and human) as disclosed.

Van Eldik et al., do not teach dual antibody (sandwich) ELISA with magnetic carrier particle and detection via luminol luminescence.

Okada et al., teach dual antibody and sandwich ELISAs wherein the antibodies are bound to a carrier comprised of a magnetic particle, see in particular Immunoassay method, column 5-6 and Example 1-9. Okada notes that the detection may be via luminol-H₂O₂ (for peroxidase), see in particular column 5, lines 47-48.

Shibue et al., teach dual antibody ELISAs wherein the immunoreactant measuring is via electrochemiluminescence in particular with the substance luminol, see in particular column 1, line 17 and Utility, columns 5-6. Shibue also notes that the invention is carried out with suitable carrier particles such as magnetic metal carrier particles, see in particular column 2, lines 40-41

Thus it would have been prima facie obvious to the skilled artisan to modify the ELISA of Van Eldik with S100 beta monoclonal antibodies using the dual antibody sandwich assay of Okada et al and Shibue using magnetic carrier immobilization and detection via chemiluminescence. One of skill in the art would have been motivated to

perform such a soluble sandwich assay using an antibody attached to a magnetic particle carrier and an antibody labeled with luminol based on the teachings of the advantages of magnetic carrier beads and luminol in isolation and detection of the immunoreactive aggregate, and the advantages in sensitivity and detection using such modifications as taught by Okada and Shibue. One of skill in the art would have expected positive results using such modification based on the positive success achieved in the Van Eldik, Okada and Shibue references and the high skill in the art of generating monoclonal antibodies and performing sandwich ELISAs. Thus, the cumulative reference teachings render the invention obvious to one skilled in the art.

Applicants argue that the claims require the use of two distinct antibodies that are specific for two distinct epitopes of the S100beta protein, one specific for an amino acid sequence of SEQ ID NO:2 and one of SEQ ID NO:3. Applicants argue that the Van Eldik reference is not enabling as the antibodies are not deposited, and their specific structure and/or specificity are not disclosed. Applicants argue that the artisan would not have been able to predict the reliable use of the antibodies in immunoassays to detect S100beta without cross-reactivity to S100. Applicants suggest that as Van Eldik is unable to describe differences in immunoreactivity of the antibodies that only a single antibody is disclosed and that Okada and Shibue cannot make up for such deficiencies as the references fail to teach antibody specificity to the noted epitopes.

Applicants arguments have been fully considered but are not persuasive. Van Eldik clearly teach two different antibodies distinguished as 1A1 and 4D4. While Van Eldik is silent as to the specific structure and epitope specificity of such monoclonals, the reference clearly establishes that the antibodies are generated from immunization with purified S100beta and are capable of specifically recognizing it. The methodology disclosed is enabling for the production of monoclonal antibody producing

hybridomas and the skilled artisan would expect such methods to produce monoclonal antibodies to all possible immunogenic epitopes within S100beta including the immunogenic epitopes as claimed, absent convincing factual evidence to the contrary. The art establishes no undue experimentation in generating such monoclonals and the artisan is well aware that sandwich assays should utilize antibodies with different epitope specificity. There is no evidence to conclude that the monoclonal antibodies are generated to the exact same epitope or that they would not be useful in the sandwich assay suggested via Okada and Shibue. Moreover, there is no reason to presume that the artisan could not easily determine from all monoclonal antibodies generated via the disclosed methods, those pairs that would be suitable in a sandwich assay for detection of S100beta. Such procedures are routine in the art as evidenced by the procedures of Van Eldik, Okada and Shibue. As set forth, the reference establishes that the antibodies react with S100beta via ELISA and do not cross-react with S100 alpha-like proteins. Thus, there is no inability of the artisan to predict the reliable use of the antibodies to detect S100beta. The evidence of record does not establish that the reference is not enabling and/or that the antibodies disclosed would not react or work in the assay as claimed. Thus, the rejection is maintained over the previously rejected claims and is newly set forth for the recited epitope structures.

Applicants argue in the response of 10-28-03 that the Action's basis implies that the Van Eldik antibodies recognize two different epitopes and thus are able to function in the assay. Applicants argue that the Action does not establish that the prior art reference is necessarily anticipatory as to the antibodies and their epitope specificity. Applicants point to the previous declaration of Dr. Aronsson describing reasons why it is felt that an artisan would not recognize the two antibodies as providing for recognition at

distinct epitopes and thus that the invention could not be found obvious for a sandwich assay in which two different antibodies with distinct specificity is required.

Applicants arguments filed 10-28-03 have been fully considered but are not persuasive. Applicants claims are directed to the peptides to which the antibodies are capable of binding and not to the epitope specificity of the monoclonals. Thus, as claimed the reference teachings anticipate the claimed invention as the S100beta peptide has both SEQ ID NO:2 and 3 and each of the monoclonals are capable of binding to a peptide having such sequences, namely S100beta. As claimed a sandwich assay is not required. In particular there is no indication that the second antibody must react with the same protein as detected by the first antibody and further there is no requirement that such reaction be at a second epitope. Nevertheless as the references are directed to a immunoassay and in particular sandwich assay the full teachings of Okada and Shibue apply. Applicants arguments are directed to limitations that are not in the instant claims.

Status of Claims

9. No claims are allowed.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.



Sharon L. Turner, Ph.D.
January 8, 2004